

# Is the (Neo)adjuvant Therapy of Patients with Primary HER2-positive Breast Cancer Cost-Covering?

Process Cost Analysis of Neoadjuvant and Post-Neoadjuvant Systemic Therapy of Patients with Primary HER2-positive Breast Cancer

## Ist die (neo-)adjuvante Therapie der Patientin mit einem HER2-positiven Mammakarzinom kostendeckend?

Prozesskostenanalyse der neoadjuvanten und postneoadjuvanten Systemtherapie von Patientinnen mit einem primären HER2-positiven Mammakarzinom



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### Key words

HER2-positive breast cancer, targeted therapy, (post-)neoadjuvant treatment, cost analysis, cost effectiveness, efficiency

### Schlüsselwörter

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### ABSTRACT

**Introduction** HER2 positivity is one of the most important predictive factors in the treatment of breast cancer patients. Thanks to new targeted anti-HER2 drugs, the prognosis for HER2-positive breast cancer patients has been significantly improved, and the treatment can now be designed according to the risk situation and the response to treatment. At the same time, these innovative targeted anti-HER2 drugs are associated with high costs and require long and involved patient care.

**Materials and Methods** In this paper, we compare the treatment costs of three post-neoadjuvant treatment regimens (trastuzumab vs. trastuzumab/pertuzumab vs. T-DM1) in early stage HER2-positive breast cancer from the perspective of the oncological outpatient clinic of a certified breast center at a university hospital, and evaluate the cost coverage.

**Results** The highest costs in systemic therapy were the material costs. These were the highest for dual blockade with trastuzumab/pertuzumab, followed by T-DM1 and trastuzumab monotherapy. According to our study, all three of these post-neoadjuvant therapy variants achieve a positive contribution margin. While all three models have similar contribution margins, the treatment pathway with T-DM1 is associated with a 30% lower contribution margin.

**Conclusions** Although these model calculations are associated with limitations in view of the introduction of biosimilar antibodies, it can be shown that modern therapeutic approaches do not always have to be associated with lower profits.

## ZUSAMMENFASSUNG

**Einleitung** Die HER2-Positivität stellt einen der wichtigsten prädiktiven Faktoren in der Therapie der Patientin mit einem Mammakarzinom dar. Dank neuer zielgerichteter Anti-HER2-Medikamente konnte die Prognose der HER2-positiven Mammakarzinompatientinnen deutlich verbessert werden und die Behandlung kann heutzutage gemäß der Risikokonstellation und des Therapieansprechens gestaltet werden. Gleichzeitig sind die innovativen zielgerichteten Anti-HER2-Medikamente mit hohen Kosten verbunden und bedürfen einer langen und intensiven Patientenbetreuung.

**Material und Methoden** Im Rahmen dieser Arbeit wurden die Therapiekosten für 3 postneoadjuvante Behandlungsschemata (Trastuzumab vs. Trastuzumab/Pertuzumab vs. T-DM1) bei

frühem HER2-positivem Mammakarzinom aus der Perspektive einer onkologischen Ambulanz des zertifizierten Brustzentrums an einer Universitätsklinik errechnet, miteinander ins Verhältnis gesetzt und die Kostendeckung wurde evaluiert.

**Ergebnisse** Die höchsten Kosten im Rahmen der Systemtherapie stellten die Sachkosten dar. Diese waren für die duale Blockade mit Trastuzumab/Pertuzumab am höchsten, gefolgt von T-DM1 und Trastuzumab mono. Alle 3 Varianten der postneoadjuvanten Therapie erzielten in unserer Untersuchung einen positiven Deckungsbeitrag. Während alle 3 Modelle ähnliche Deckungsbeiträge aufweisen, ist der Therapieweg mit T-DM1 mit einem 30% niedrigeren Deckungsbeitrag verbunden.

**Schlussfolgerungen** Wenngleich vor dem Hintergrund der Einführung von biosimilaren Antikörpern diese Modellrechnungen mit Limitationen verbunden sind, kann gezeigt werden, dass moderne Therapieansätze durchaus nicht immer mit geringeren Gewinnen verbunden sein müssen.

## Introduction

Breast cancer is the most common tumor affecting women worldwide. However, in recent years the prognosis has improved somewhat, especially in patients with HER2-positive tumors, due to targeted antibody therapies. Patients with HER2-positive primary breast cancer usually receive neoadjuvant therapy that includes the so-called dual blockade with trastuzumab and pertuzumab—depending on age, comorbidities, tumor size, and nodal status [1]. Depending on the achievement of pathological complete remission (pCR), a one-year maintenance therapy with trastuzumab, trastuzumab and pertuzumab, or T-DM1 [2] is then performed in the post-neoadjuvant setting. In view of the steadily increasing costs in the healthcare system, it is important to evaluate the targeted therapy within this special subgroup as it accounts for a high proportion of the costs. In this context, the question of cost coverage also arises for service providers, in particular for the certified breast centers that perform the majority of neoadjuvant and post-neoadjuvant therapies.

Due to demographic developments in Germany and also to changes in lifestyle, cancer continues to increase. With regard to the tumors affecting women, breast cancer is by far the most common cancer, with an incidence of approx. 69 000 cases per year [3]. It is also the most common malignant disease in Germany. With regard to mortality, breast cancer in particular has a high cure rate. Nevertheless, more than 17 000 women die each year as a result of metastatic breast cancer. Over the past three decades, however, the prognosis has improved both internationally and nationally, and there has been a reduction in mortality [4]. In addition to the introduction of screening, provision of care in certified facilities, and increasing compliance with guidelines, one of the main causes of this is the optimization of systemic therapy. While the subgroup of HER2-positive breast cancers per se has a poor prognosis overall, through the neoadjuvant and post-neoad-

juvant use of new targeted therapies it has been possible to achieve a very significant improvement in prognosis for these subtypes [5]. Thus, a poor prognostic parameter has become a reliable predictive marker. A milestone was the introduction of the dual blockade with trastuzumab and pertuzumab in the neoadjuvant context. As a result, the pCR rate increased to up to 90% [6]. Since the pCR rate correlates with the prognosis for the disease, especially in the case of HER2-positive breast cancer, efforts are now concentrated primarily on so-called post-neoadjuvant therapy. While the classic maintenance therapy following neoadjuvant HER2-targeted therapy consisted of the administration of trastuzumab for one year in total (possibly in combination with endocrine therapy in the case of simultaneous hormone receptor positivity), today there is a consensus, in analogy to the purely adjuvant APHINITY study [7], that the one-year dual blockade with trastuzumab and pertuzumab should be recommended for patients who are at increased risk (e.g., nodal positivity). As we go down the path towards individualized therapy, in addition to the APHINITY study mentioned above, the recently published KATHERINE study has also “practice changing” delivered results [8]. In this post-neoadjuvant trial, a significant advantage in invasive disease-free survival (IDFS) was observed in non-pCR patients if, after neoadjuvant treatment, they received the antibody-chemotherapy conjugate T-DM1 for one year instead of the standard trastuzumab. So far, it remains unclear whether the therapy with T-DM1 is better or equally effective as therapy with dual blockade. All three targeted therapies have low overall toxicity and a very good therapeutic index. Nowadays, the customized therapy described above is regarded worldwide as the standard [9].

In this context and in view of the associated increase in therapy costs as well as the need for comprehensive care, health economics issues play an increasingly important role—especially for the

group of HER2-positive breast cancer patients who require the costly antibody therapies mentioned above.

The majority of neoadjuvant and adjuvant therapies are carried out in breast centers certified according to the criteria of the German Cancer Society (Deutsche Krebsgesellschaft e. V.), and according to the ÄKZert certification body in North Rhine-Westphalia. Due to the increasing cost pressures, including a shift of surgical therapies to the outpatient setting, cuts to services provided by the medical service of the health insurance providers, and the provision of uncompensated services (psycho-oncology, interdisciplinary tumor conferences, etc.) required under the certification criteria, each center is faced with the question as to whether systemic therapies can be provided in a way that enables the costs to be covered.

Accordingly, the cost situation for the two innovative anti-HER2 therapies (dual blockade and T-DM1) compared to the long-standing standard trastuzumab monotherapy is significant for both the service provider and cost bearer. Within the scope of this publication, we calculated and compared the treatment costs of all three treatment regimens from the perspective of the oncological outpatient clinic of a certified breast center at a university hospital, and evaluated the cost coverage. The analysis refers to the costs of both neoadjuvant and post-neoadjuvant treatment.

## Materials and Methods

The analysis of the three therapy options was performed using software-based process-related health economics analysis ("Softwarebasierte Prozessuale Gesundheitsökonomische Analyse" [SPGA]). For this purpose, the differences between the three variants were investigated in detail at the process level in neoadjuvant and post-neoadjuvant systemic therapy (► **Fig. 1 a**). In the context of calculating process costs on a full costs basis, the consumption of personnel, material and infrastructure resources was calculated according to the treatment processes. The personnel costs of the processes were based on the gross hourly wages of the organizational units involved (TV-L). The cost data were based on the audited annual financial statements for 2017. As a result, we were able to make an overall comparison of the process durations and process costs of the three therapy options so as to assess the degree of cost coverage.

### Project organization

As a starting point for the analysis, we obtained precise definitions of the respective therapy options from the responsible service provider, and identified all of the services and organizational units involved in implementation over the course of the therapy. Based on the treatment concepts, detailed process documentation, including process durations, was created by a special software program in a fully automated manner; the organizational units involved in the process merely had to check this documentation. The goal of this process modeling was to create genuine transparency around the performance of services. This was followed by an evaluation of the analyzed processes, with costs that were already available from the existing business analysis data and from the clinic's financial controlling. In addition to the direct personnel costs from the treatment processes, there were individual costs

for drug consumption; these play a special role in the neo-adjuvant and post-neoadjuvant systemic therapy of HER2-positive breast cancer. The cost accounting was completed with causal allocation of direct and indirect personnel and material costs for the facility.

Similar to cost unit accounting, process cost accounting shows the total costs for each case on a full costs basis, but with a special focus on the processes, so that the costs for each individual sub-process can be presented transparently. Accordingly, in addition to transparency around the costs of individual service areas, the software-based process-related health economics analysis also provides answers to key questions, such as:

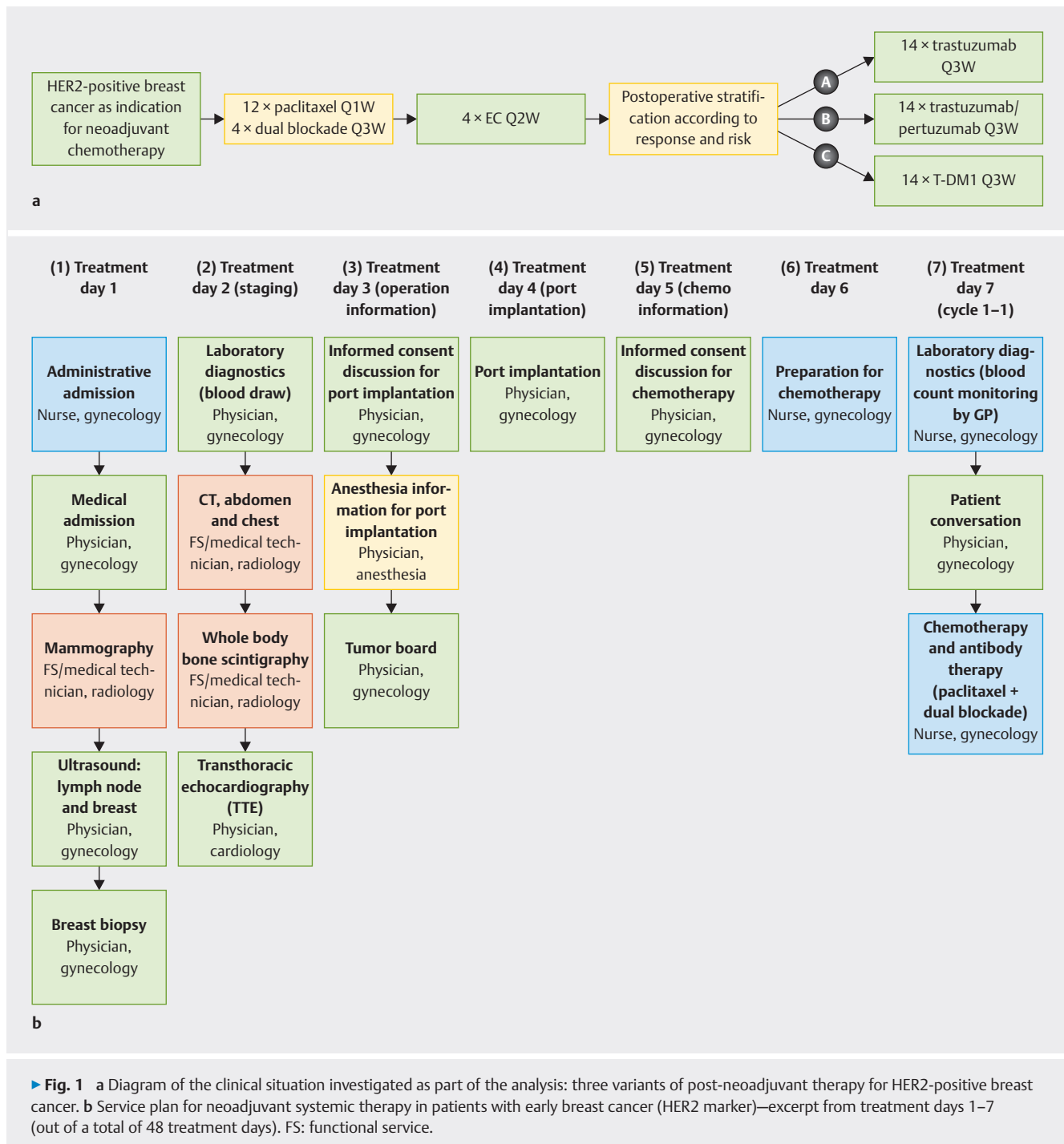
- What is the cost of medical admission?
- How intensively are doctors and nurses involved in the treatment?
- How much do individual services or processes cost?

### Determining core competencies

In the context of determining core competencies, the treatment concept favored by the institution for neoadjuvant systemic therapy in patients with early breast cancer (HER2 marker) was initially defined by the responsible physician. This involved defining the entire range of services, i.e., the planned services and specific methods for each individual treatment day, as well as the responsible department/ward or service facility. These services include, in particular, mammography, breast ultrasound with subsequent biopsy, laboratory diagnostics (follow-up checks are carried out by the patient's GP), transthoracic echocardiography (TTE), port implantation, and the interdisciplinary tumor board. Services that are not originally part of the outpatient service concept (lumpectomy) or that are performed by external service providers (radiotherapy) were excluded, both from the core competencies and thus also from the cost calculation, as well as from the consideration of the revenue.

A total of three phases were planned for the duration of the therapy. The first phase consists of 12 cycles starting with chemotherapy and antibody therapy with paclitaxel and dual blockade (trastuzumab with pertuzumab) in a 21-day treatment interval alternating with chemotherapy with paclitaxel in a 7-day treatment interval, amounting to a total of 4 cycles with paclitaxel and dual blockade and 8 cycles with paclitaxel only. The second phase consists of 4 cycles of chemotherapy with epirubicin and cyclophosphamide in a 14-day treatment interval (dose-dense). Finally, the third phase (about 1 year) consists of an antibody therapy with trastuzumab over 14 cycles in a treatment interval of 21 days (cf. ► **Fig. 1**).

Based on the core competence described, two further variants were calculated for the comparative analysis: administration for a total of one year of the dual blockade with trastuzumab and pertuzumab (after surgery, for example in the case of positive lymph nodes prior to therapy), and administration for one year of the antibody-chemotherapy conjugate T-DM1 instead of the standard trastuzumab (after surgery without complete remission).



## Process modeling and processing of financial controlling data

For each service, detailed process modeling was then generated; after a review of the organizational units performing the service and an evaluation including execution times, this provides a complete trail covering the full duration of the therapy.

In parallel with the modelling, the facility's Controlling department provided relevant data for the process cost accounting. These include cost data (expenses of the relevant cost centers),

personnel data (gross hourly rates for the relevant organizational units), performance data (case numbers, care days or credit points), and materials data (pharmacy drug prices at the gross purchase price), which merely had to be exported from the existing systems and made available in raw form for further processing.

In addition to various descriptive representations of the processes (core competence profile, process flow chart, swimlane dia-

gram), the ClipMed software provided a detailed process cost report in conjunction with the process data.

## Results

The process cost results can be visualized in different degrees of detail and according to different perspectives.

### Total cost view

The analysis of the different types of costs shows that the material costs account for the majority of the total costs. The material costs consist of pharmaceutical costs plus the cost of other materials, with pharmaceutical costs accounting for over 90% of the overall material costs. As an example, the pharmaceutical costs for the standard procedure come to € 90355.55, while cost of other materials amounts to € 1505.35. Since the costs for other materials are the same across all therapy methods and only the drug costs vary, the drug costs for the therapy method with dual blockade can be estimated at € 145386.54, and the drug costs for the therapy method with T-DM1 can be estimated at € 135731.93.

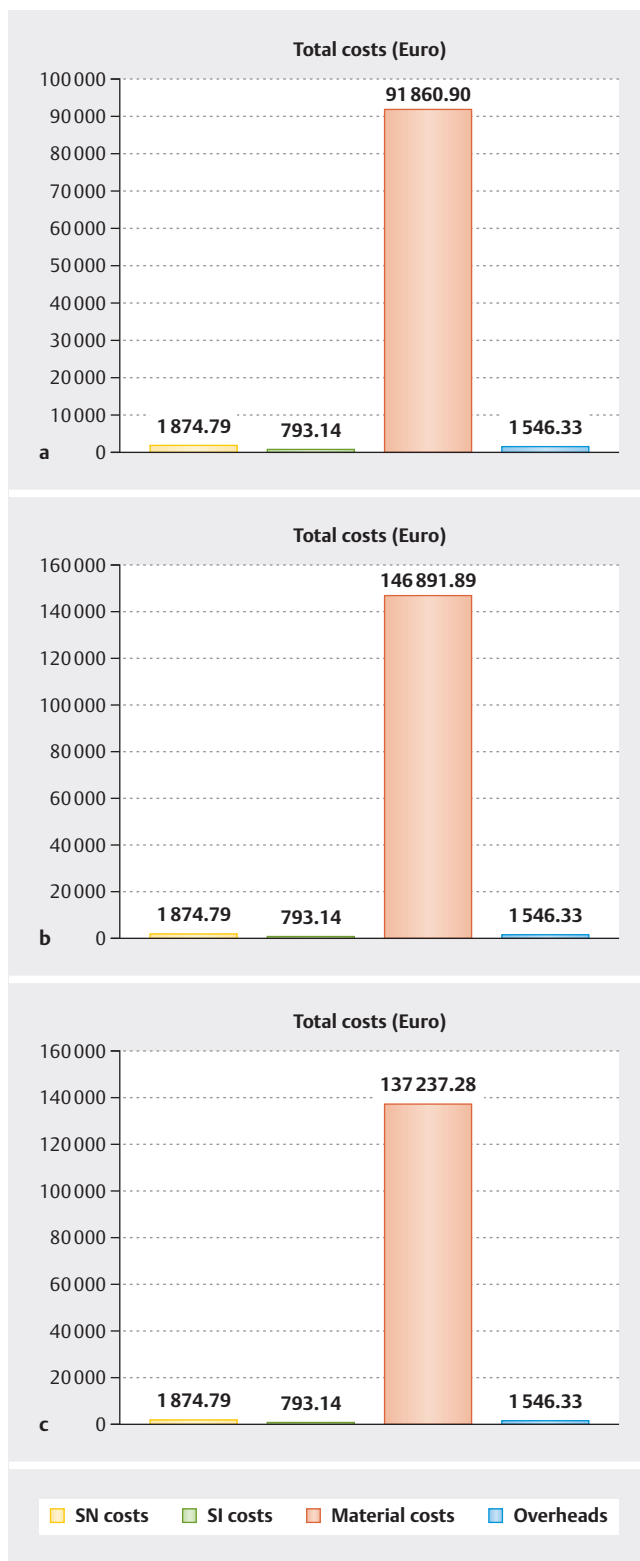
Since the processes of the various therapy methods also do not differ in terms of their utilization of personnel resources, the direct personnel costs amount to € 1874.79. These costs, which are also referred to as service quantity induced (SI) costs, include all personnel process costs that are directly related to the direct provision of the service to a patient. Personnel process costs that arise without a direct link to a patient are referred to as service quantity neutral (SN) costs. These include, for example, the implementation of hygiene measures or the attendance of continuing education and training. These costs must be taken into account on a prorata basis for each patient; they amount to € 793.14.

In addition to the direct personnel and materials costs, there are also the indirect costs of the medical and non-medical infrastructure in the amount of € 1546.33, termed overheads, which complete the process cost accounting to reflect full cost accounting (cf. ▶ Fig. 2).

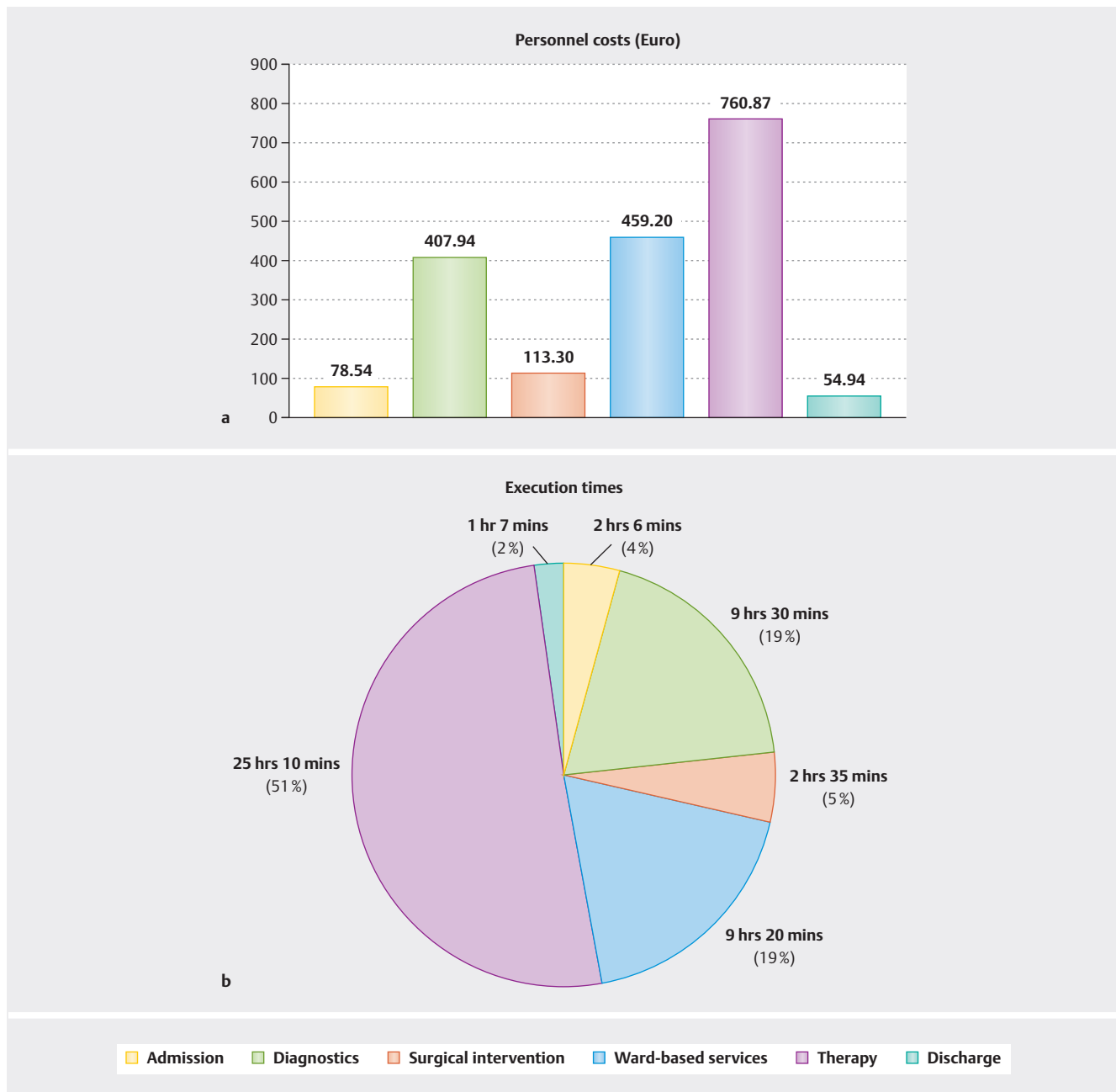
### Process view

With regard to the processes, it is possible to visualize the distribution of personnel costs between the various sections of the treatment process. The terminology for the business processes was originally based on the inpatient procedure, but here it refers to the provision of the defined core competence from the first to the last day of treatment. Admission and discharge also include medical services, such as a physical examination or a final conversation. Port implantation is considered to be a surgical intervention. Ward-based services predominantly include doctor-patient contact. The majority of personnel costs are incurred in the context of chemotherapy cycles, amounting to € 760.87 and € 459.20. This is followed immediately by diagnostics (mammography, CT, bone scintigraphy, etc.), amounting to € 407.94 (cf. ▶ Fig. 3 a).

The process view of the execution times of the business processes shows the distribution of all personnel times, from the start of treatment to the end of treatment. In addition to the more extensive diagnostics at 9 hours and 30 minutes, at 9 hours and 20 minutes the ward-based services, including in particular the



▶ Fig. 2 Total costs, including personnel costs, of neoadjuvant systemic therapy in patients with early breast cancer (HER2 marker). a Standard therapy procedures (post-neoadjuvant trastuzumab monotherapy over 1 year), b Dual blockade 1 year post-neoadjuvant, c T-DM1 1 year post-neoadjuvant. SI costs: service quantity induced costs, SN costs: service quantity neutral costs.



► **Fig. 3** Personnel costs (a) and execution times (b) for the business processes of neoadjuvant systemic therapy in patients with early breast cancer (HER2 marker) in the standard therapy procedure (post-neoadjuvant trastuzumab monotherapy over 1 year).

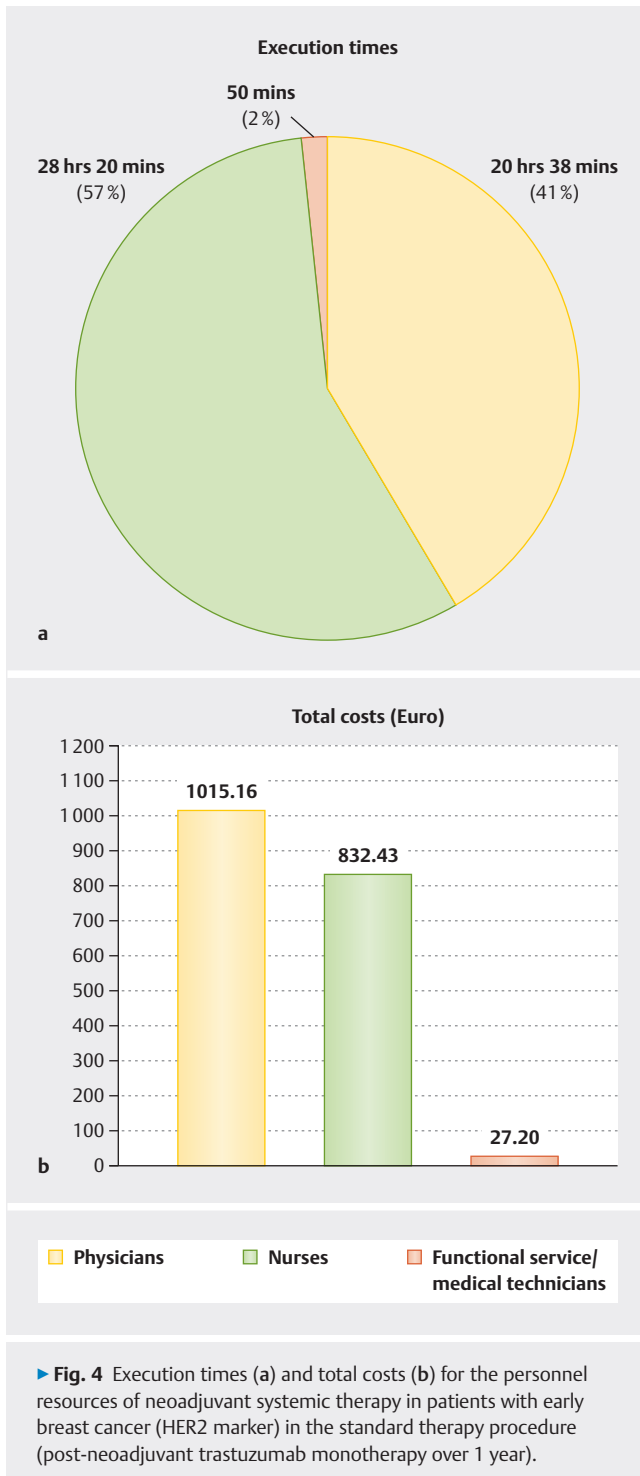
patient conversations, also take up a large part of the time. However, the largest part is accounted for by the treatment itself, at 25 hours and 10 minutes; this predominantly involves the chemotherapy and antibody therapy (cf. ► **Fig. 3b**).

### Resources view

In addition to the process view, the distribution of execution times and costs can also be visualized according to personnel resources, either for each individual organizational unit involved in the process, or summarized according to occupational groups.

The distribution of the process execution times according to personnel resources shows the relationship between the three occupational groups involved: physicians, nursing service, and functional service/medical technicians (cf. ► **Fig. 4a**). As already shown in the depiction of the execution times according to business processes, the nursing service is mainly responsible for implementing the therapy, at 28 hours and 20 minutes, while the physicians also account for a large part of the processes at 20 hours and 38 minutes, mainly in the area of ward-based services, but also distributed proportionally among all other business processes. The mapping of costs according to personnel resources is as follows: first





are the physicians at € 1015.16, then the nursing service at € 832.43. The functional service in the context of surgical intervention accounts for only a small part, at € 27.20 (cf. ▶ Fig. 4 b).

### Overhead costs view

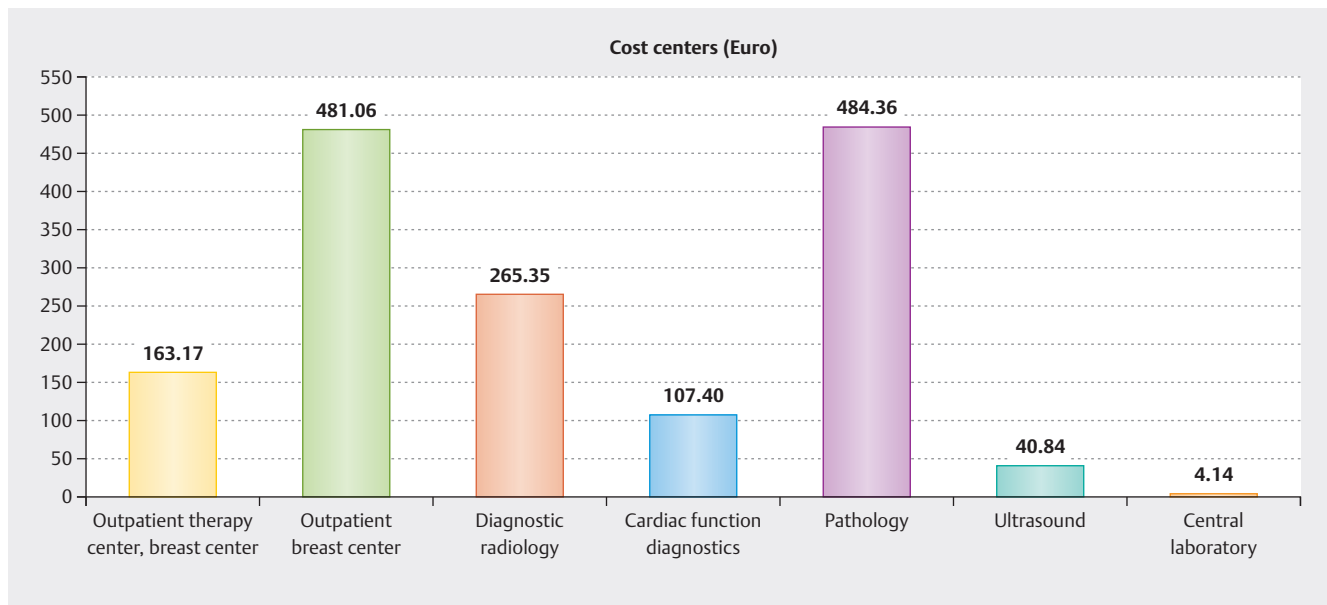
While the process costs or personnel costs shown above only constitute partial costs within the process cost accounting, the material costs and overheads complete these to reflect the full costs. The overheads consist of the medical and non-medical infrastructure costs for all of the cost centers involved (see ▶ Fig. 5). In addition, other personnel costs can also be included if these come from organizational units of the cost centers providing the services that were not calculated in relation to the processes, because no detailed controlling data was available or because the type of process does not allow a clear assignment to a patient (e.g., laboratory diagnostics). These include, for example, radiology or pathology.

### Revenue view

A look at the total costs in comparison with the per-case revenue shows that, in principle, all variants achieve a positive contribution margin. In comparing the contribution margins, none of the variants are significantly more cost-effective than the others, since the contribution margins are almost identical in relation to total costs and total revenue (cf. ▶ Fig. 6); only for the TDM-1 variant is the contribution margin about 30% lower. The composition of the revenues is set out in ▶ Table 1.

### Discussion

Especially for patients with the HER2-positive breast cancers, in recent years there has been a shift in systemic treatment from adjuvant to neoadjuvant therapy. This is mostly due to the increase in the rate of pathological complete remissions under the dual blockade with trastuzumab and pertuzumab. In addition, several analyses have shown that the increased pCR rate is associated with improved survival (EFS) [10]. Subsequently, in the APHINITY study, it was observed that patients at higher risk who received dual blockade in the adjuvant setting had a survival advantage over trastuzumab therapy alone [11]. The results of the KATHERINE study then led to a further paradigm shift; these results showed that changing post-neoadjuvant therapy from trastuzumab monotherapy for one year to one-year therapy with T-DM1 is associated with a significant survival advantage [8]. For this reason, national and international guidelines currently recommend that low-risk patients with pathological complete remission be treated with trastuzumab monotherapy, and that dual blockade for one year be given to patients at increased risk, e.g., with nodal positivity. Conversely, if pathological complete remission is not achieved, therapy with T-DM1 should now be carried out for one year as standard.

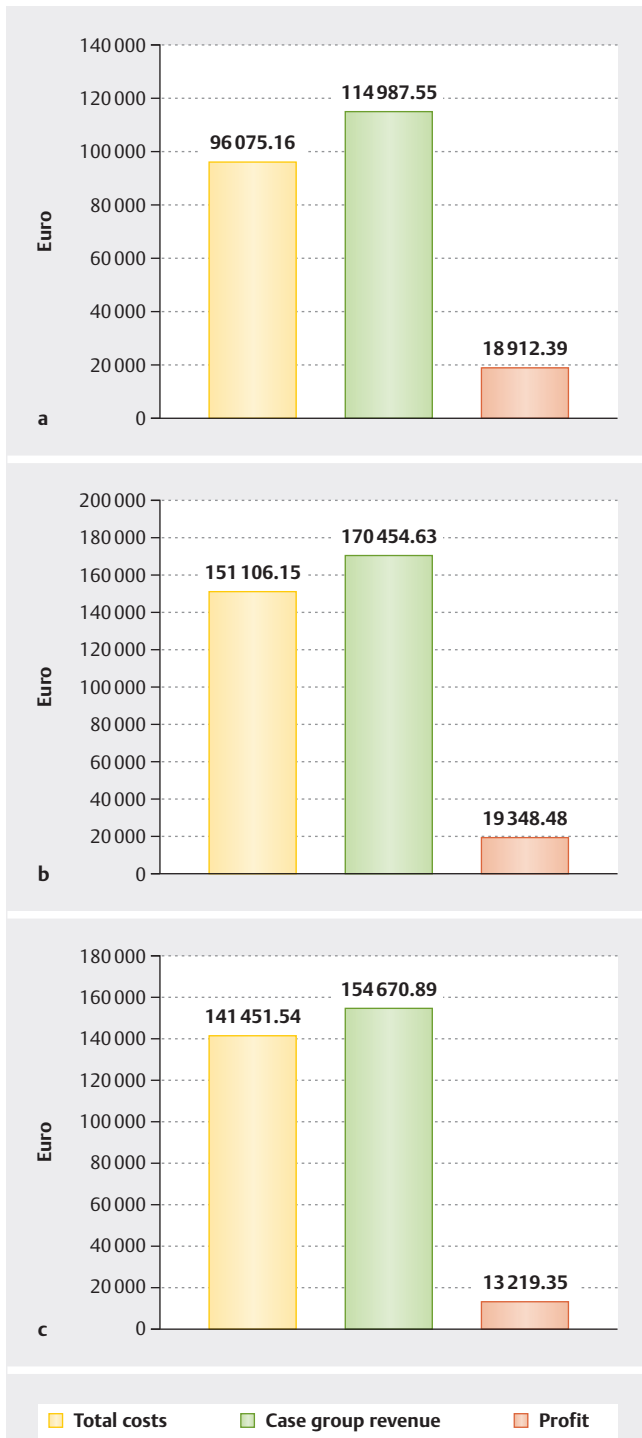


► **Fig. 5** Distribution of overheads according to cost centers for neoadjuvant systemic therapy in patients with early breast cancer (HER2 marker) in the standard therapy procedure (post-neoadjuvant trastuzumab monotherapy over 1 year).

► **Table 1** Summary of the total revenue from neoadjuvant and post-neoadjuvant systemic therapy in patients with early breast cancer (HER2 marker).

Service	EBM code	EBM revenue	Number	Total revenue
Mammography	34270	€ 28.23	1	€ 28.23
Breast biopsy	19320; 08320; 19322	€ 127.01	1	€ 127.01
Breast ultrasound	33041	€ 17.47	3	€ 52.41
Laboratory diagnostics (blood draw before port implantation)	32120; 32081; 32083 etc.	€ 6.60	1	€ 6.60
CT, abdomen and chest	34341; 34330	€ 157.58	1	€ 157.58
Whole body bone scintigraphy	17210; 17311; 17312	€ 97.39	1	€ 97.39
Transthoracic echocardiography (TTE)	33022	€ 35.80	6	€ 214.80
Anesthesia information for port implantation	05310	€ 19.07	1	€ 19.07
Port implantation	8999; 31212; 05350; 31822	€ 540.77	1	€ 540.77
Basic flat rate for gynecology	08211	€ 15.45	4	€ 61.80
Supplementary flat rate for oncology	08345	€ 20.35	4	€ 81.40
Infusion	02100	€ 6.07	34	€ 206.38
Medication pump	02120	€ 12.47	1	€ 12.47
Drugs for standard therapy (trastuzumab)				€ 113381.64
Drugs T-DM1				€ 153064.98
Drugs for dual blockade (trastuzumab/pertuzumab)				€ 168848.72
<b>Total revenue from standard therapy</b>				<b>€ 114987.55</b>
<b>Total revenue from therapy with T-DM1</b>				<b>€ 154670.89</b>
<b>Total revenue from therapy with dual blockade</b>				<b>€ 170454.63</b>





► **Fig. 6** Contribution margin for neoadjuvant systemic therapy in patients with early breast cancer (HER2 marker, total costs compared to case group revenue). **a** Standard therapy procedures (post-neoadjuvant trastuzumab monotherapy over 1 year), **b** dual blockade 1 year post-neoadjuvant, **c** T-DM1 1 year post-neoadjuvant.

A problem that repeatedly arises in this context is the increase in costs due to the sometimes expensive targeted therapeutic approaches. In particular, monoclonal antibodies are by far among the most expensive oncological agents. In light of the limited resources in the health sector, it makes sense to take a health economics view. The aim of this analysis is to compare the costs of neoadjuvant HER2-targeted therapy as well as post-neoadjuvant monotherapy therapy with trastuzumab, dual antibody therapy with trastuzumab and pertuzumab, and monotherapy with T-DM1. With regard to the cost coverage for the three variants, it must be added as a critical note that the positive contribution margin was only obtained under the planned optimal conditions, in the situation and with the structures and processes shown, for the year analyzed. As soon as there are deviations in the standard processes or structures or changes in the material and personnel costs, whether due to services that are without result or services that lead to the wrong result, this can potentially lead to a significant reduction in the contribution margin.

The question of the cost-effectiveness of innovative neoadjuvant, adjuvant, and post-neoadjuvant targeted combination therapies in the group of primary HER-2 positive breast cancer patients has already been investigated internationally. In the analysis by Kunst et al., the data from the KATHERINE study mentioned above and other available evidence to date, as well as the epidemiological data registers, were evaluated according to their current status with regard to efficiency, oncological effectiveness, and influence on the patients' quality of life [12]. This analysis based on a theoretical model showed that neoadjuvant chemotherapy with paclitaxel and dual blockade (THP), followed by trastuzumab monotherapy in the case of pCR or T-DM1 in the absence of complete remission, was most effective in relation to all three parameters investigated. This analysis did not include a comparison of the dual blockade as post-neoadjuvant treatment. It should also be noted critically that to date the neoadjuvant THP regimen has only been investigated in the ADAPT HER2+/HR study [13]; accordingly, this regimen does not yet represent a neoadjuvant treatment standard, although the very good survival data from the study, published recently, could influence this in the future [14, 15]. In the currently recruiting international Phase II CompassHER2-pCR (NCT04266249) and DECRESCENDO (NCT04675827) studies, this combination is investigated further as a de-escalation regimen in the neoadjuvant setting. Similar results were obtained in the analysis by Hasset et al., who also evaluated different neoadjuvant anti-HER2 therapies followed by post-neoadjuvant treatment adapted to the response, with Herceptin monotherapy, dual blockade, or T-DM1, in terms of cost-efficiency, quality of life, and oncological efficacy [16]. This analysis is also based on the theoretical model and shows that optimum cost-efficiency is achieved by the neoadjuvant THP or TH regimen. However, this study focuses mainly on the comparison of different neoadjuvant regimens, and less on postoperative therapies. Furthermore, the two abovementioned analyses provided a direct comparison of the drug costs, and not a comparison of the process costs and the contribution margins of the health insurance providers. While this is understandable in view of the completely different health systems, it makes comparison with our own results more difficult. At the same time, the abovementioned publications show the increasing

relevance of health economics issues in senology, especially in the group of HER2-positive breast cancer patients.

In Europe, 2.45 million people develop cancer every year [17]. Breast cancer is the most common cancer affecting women in Europe. In total, costs of € 126 billion per year are incurred in the EU as a result of oncological diseases, of which € 28.4 billion is for inpatient care. Breast cancer not only represents a major diagnostic and therapeutic challenge for the various service providers, it also has considerable implications in terms of health economics due to its high incidence. The diagnosis, therapy, and follow-up care of patients with breast cancer requires an extremely complex, time-consuming, and labor-intensive range of services, such as is required in this form for hardly any other disease. On average, € 13 per inhabitant per year is spent on breast cancer in the European Union. In countries such as Lithuania and Bulgaria, € 2 per inhabitant per year is spent on breast cancer. In comparison, in Germany this figure is € 29 per inhabitant per year [17]. Furthermore, expenditure on healthcare services in Germany has been rising steadily for years. The reasons for the increase in expenditure are the continuous expansion of the diagnostic, medical, and nursing services on offer, and in particular the rising costs of new, innovative medicines. In addition, there are epidemiological challenges and demographic developments. While currently 21% of the population is older than 65, by 2050 this figure will be 33% [18]. This means that the patient cohort is growing, giving rise to healthcare costs, while at the same time the healthy population that is paying into the coffers of the health insurance providers is shrinking. However, since a continuous increase in health insurance contributions and non-wage labor costs to finance the health system generally meets with poor acceptance, it is necessary to consider things from the expenditure side.

A further question that arises at the moment and is much discussed is whether the service providers are still able to implement innovative therapies in a manner which allows for cost coverage. Although providing care in certified center structures is particularly important in the healthcare sector, funding continues to be a problem that often remains unresolved [19, 20]. The certified centers require additional human and material resources in order to meet the required quality parameters. On the other hand, the more compact delivery of inpatient services, reduced revenue due to reduced length of inpatients stays, and the lack of mapping of complex surgical interventions are all part of the currently increasing cost pressure in the healthcare sector. In the context of examinations by the medical service of the health insurance providers, days of patients' inpatient stays are increasingly not being recognized, which means they fall below the lower limit for the length of stay. From the point of view of the cost bearers, aspects such as psycho-oncological care, radioactive labelling in sentinel node biopsy, discussions with patients and their relatives, sociomedical advice, and other care offerings do not justify an inpatient stay. This holistic concept of oncological care is very difficult to assure during inpatient stays of just a few days or in the outpatient setting due to the lack of comprehensive networks, especially for certified centers. Several publications have already shown that care in certified breast cancer centers is not adequately remunerated, and supplements are necessary so that the work can be performed in a manner that enables the costs to be covered [21].

The main problem is the lack of reimbursement of certain costs. These include expenses for (re-)certification as well as costs for fulfilling mandatory quality criteria such as training, professional development and continuing education [22], research involving molecular and clinical studies, center coordination, additional support for patients and their families (e.g., social services, psycho-oncology), and provision of infrastructure for interdisciplinary partners, as well as, in particular, quality assurance and documentation. Thus, if the surgical therapy of a patient with breast cancer is difficult to perform in a manner that will allow the costs to be covered, the question arises as to whether this is possible for the systemic therapies, in particular for the costly antibody therapy of a patient with HER2-positive breast cancer. In this study we were able to show that, at least for one university service provider, all three treatment regimens achieve a positive contribution margin, without any of the compared variants being significantly more cost-effective than the others (► Fig. 2).

However, the analysis also has limitations, which should be taken into account when interpreting the results. A limitation of the present analysis is that it does not include trastuzumab biosimilar antibodies, nor does it include the subcutaneous administration forms of Herceptin and Herceptin/Perjeta (Phesgo). The first group has meanwhile led to a significant reduction in costs, with five preparations now approved by the EMA [23]. However, there is still potential for further cost reduction in the German healthcare system. A recent publication used the example of trastuzumab to show that a further 95.9 to 120.5 million Euros per year could be saved if all patients received the cheapest trastuzumab biosimilar compared to the originator product [24]. Currently, the influence and market share of the subcutaneous preparations is not clearly foreseeable [25, 26]. However, it should be noted that in almost all oncological facilities the therapies have been completely or predominantly switched to biosimilar antibodies; therefore, no changes are to be expected in the relative overall result.

At the same time, however, in the context of conserving resources in times of the COVID-19 pandemic, the protection of patients from mutual contagion and the achievable advantage of other therapies being performed during this time, which can count against the result, constitute an effect that should not be underestimated in this kind of analysis.

The fact that this analysis was carried out in the specific setting of a university hospital is another aspect that needs to be considered when interpreting our results. It is possible that similar studies would lead to different results for another service provider, e.g., a medical practice, Medical Care Center (MVZ) or non-university hospital with corresponding authorization—or in another setting, such as specialist outpatient care (ASV).

Compared to the results of Kunst et al. and Hasset et al., the authors of the two abovementioned analyses used a Markov model and, in addition to the purely therapeutic costs, also took into account the patient's quality of life and possible costs in the event of a recurrence [12, 16]. We did not carry out these complex analyses in the present study; instead, we focused specifically on the treatment costs in Germany.

This is also one of the strengths of our study, in which we present, for the first time, valid socio-economic figures for these

therapies that are standard in the German healthcare system. They demonstrate that, at least for the present, certified breast centers are able to provide comprehensive, modern antibody therapies in a manner that assures cost coverage. However, legal, structural, and financial changes can jeopardize this cost coverage at any time.

## Conclusion

HER2 positivity serves as one of the most important predictive markers in breast cancer, and enables risk-adapted, targeted anti-HER2 therapy to be performed in this cohort of patients. At the same time, the highly effective modern anti-HER2 agents are associated with high costs. In the setting of a certified university breast center, a positive contribution margin can nevertheless be achieved in this context, without any one of the post-neoadjuvant therapy regimens having a significantly higher or lower contribution margin than the others.

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## Conflict of Interest

N. Krawczyk and M. Osygus declare that they have no conflicts of interest. E. Ruckhäberle received fees from AMGEN, Roche, Celgene, Pfizer, Novartis, AstraZeneca, MSD, TEVA, TESARO, Pharma Mar, Pierre Fabre, Janssen-Cilag, Clovis Oncology, GSK, and Exact Sciences for lectures and consultancy work. M. Lux received fees from Lilly, Roche, AstraZeneca, MSD, Novartis, Pfizer, Eisai, Exact Sciences, Daiichi Sankyo, Grünenthal, Gilead, Pierre Fabre, PharmaMar, and Roche for lectures and consultancy work; travel expenses reimbursed by Roche and Pfizer; M. Lux is a member of the editorial board of medac. The University Hospital of Düsseldorf received fees from Roche, Pfizer, Novartis, AstraZeneca, TEVA, MSD, Daiichi Sankyo, and Onkowissen for lectures and consultancy work by T. Fehm. M. Greiling is the scientific director of software-based academic continuing education with a university certificate as Certified Workflow Manager in Health Care with the ClipMed PPM web application. / N. Krawczyk and M. Osygus erklären, dass kein Interessenkonflikt besteht. E. Ruckhäberle erhielt für Vorträge bzw. Beratungstätigkeit Honorare von AMGEN, Roche, Celgene, Pfizer, Novartis, AstraZeneca, MSD, TEVA, TESARO, Pharma Mar, Pierre Fabre, Janssen-Cilag, Clovis Oncology, GSK, Exact Sciences. M. Lux erhielt für Vorträge bzw. Beratungstätigkeit Honorare von Lilly, Roche, AstraZeneca, MSD, Novartis, Pfizer, Eisai, Exact Sciences, Daiichi Sankyo, Grünenthal, Gilead, Pierre Fabre, PharmaMar und Roche; Reisekostenerstattung von Roche und Pfizer; M. Lux ist Mitglied des Editorialboards von medac. Das Universitätsklinikum Düsseldorf erhielt für Vorträge bzw. Beratungstätigkeit durch T. Fehm Honorare von Roche, Pfizer, Novartis, AstraZeneca, TEVA, MSD, Daiichi Sankyo, und Onkowissen. M. Greiling ist wissenschaftlicher Leiter der softwarebasierten akademischen Weiterbildung mit Hochschulzertifikat zum Certified Workflow-Manager in Health Care mit der ClipMed PPM Web-Applikation.

## References/Literatur

- [1] Ditsch N, Untch M, Kolberg-Liedtke C et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2020. *Breast Care (Basel)* 2020; 15: 294–309. doi:10.1159/000508736
- [2] Schneeweiss A, Bauerfeind I, Fehm T et al. Therapy Algorithms for the Diagnosis and Treatment of Patients with Early and Advanced Breast Cancer. *Breast Care (Basel)* 2020; 15: 608–618. doi:10.1159/000511925
- [3] Robert Koch Institut, Zentrum für Krebsregisterdaten, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.. *Krebs in Deutschland 2015/2016*. 2019. Accessed August 18, 2022 at: [https://edoc.rki.de/bitstream/handle/176904/6012.3/krebs\\_in\\_deutschland\\_2019\\_2.pdf?sequence=6&isAllowed=y](https://edoc.rki.de/bitstream/handle/176904/6012.3/krebs_in_deutschland_2019_2.pdf?sequence=6&isAllowed=y)
- [4] Malvezzi M, Carioli G, Bertuccio P et al. European cancer mortality predictions for the year 2019 with focus on breast cancer. *Ann Oncol* 2019; 30: 781–787. doi:10.1093/annonc/mdz051
- [5] Kümler I, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2-positive breast cancer. *Cancer Treat Rev* 2014; 40: 259–270. doi:10.1016/j.ctrv.2013.09.002
- [6] Loibl S, Gianni L. HER2-positive breast cancer. *Lancet* 2017; 389: 2415–2429. doi:10.1016/S0140-6736(16)32417-5
- [7] von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017; 377: 122–131. doi:10.1056/NEJMoa1703643
- [8] von Minckwitz G, Huang CS, Mano MS et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2019; 380: 617–628. doi:10.1056/NEJMoa1814017
- [9] Pusztai L, Foldi J, Dhawan A et al. Changing frameworks in treatment sequencing of triple-negative and HER2-positive, early-stage breast cancers. *Lancet Oncol* 2019; 20: e390–e396. doi:10.1016/S1470-2045(19)30158-5
- [10] Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014; 384: 164–172. doi:10.1016/S0140-6736(13)62422-8
- [11] Piccart M, Procter M, Fumagalli D et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-up. *J Clin Oncol* 2021; 39: 1448–1457. doi:10.1200/JCO.2020.01204
- [12] Kunst N, Wang SY, Hood A et al. Cost-Effectiveness of Neoadjuvant-Adjuvant Treatment Strategies for Women With ERBB2 (HER2)-Positive Breast Cancer. *JAMA Netw Open* 2020; 3: e2027074. doi:10.1001/jamanetworkopen.2020.27074
- [13] Nitz UA, Gluz O, Christgen M et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab +/- weekly paclitaxel. *Ann Oncol* 2017; 28: 2768–2772. doi:10.1016/j.annonc.2021.12.008
- [14] Fehm TN, Stickeler E, Fasching PA et al. Update Breast Cancer 2021 Part 3 – Current Developments in the Treatment of Early Breast Cancer: Review and Assessment of Specialised Treatment Scenarios by an International Expert Panel. *Geburtshilfe Frauenheilkd* 2021; 81: 654–665. doi:10.1055/a-1487-7642
- [15] Nitz U, Gluz O, Graeser M et al. De-escalated neoadjuvant pertuzumab plus trastuzumab therapy with or without weekly paclitaxel in HER2-positive, hormone receptor-negative, early breast cancer (WSG-ADAPT-HER2+/HR-): survival outcomes from a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2022; 23: 625–635. doi:10.1016/S1470-2045(22)00159-0

- [16] Hassett MJ, Li H, Burstein HJ et al. Neoadjuvant treatment strategies for HER2-positive breast cancer: cost-effectiveness and quality of life outcomes. *Breast Cancer Res Treat* 2020; 181: 43–51. doi:10.1007/s10549-020-05587-5
- [17] Luengo-Fernandez R, Leal J, Gray A et al. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* 2013; 14: 1165–1174. doi:10.1016/S1470-2045(13)70442-X
- [18] de la Maisonnette C, Oliveira Martins J. Public Spending on Health and Long-term Care: A new set of projections. Paris: OECD Publishing; 2013.
- [19] Lux MP, Nabieva N, Hartkopf AD et al. Therapy Landscape in Patients with Metastatic HER2-Positive Breast Cancer: Data from the PRAEGNANT Real-World Breast Cancer Registry. *Cancers (Basel)* 2018; 11: 10. doi:10.3390/cancers11010010
- [20] Lux MP, Beckmann MW. Organzentren und Zertifizierung: Chancen und Probleme. Wallwiener D, Grischke EM, Grischke S, Taran FA, Bastert G (eds.). *Gynäkologische Onkologie. Begründet von Heinrich Schmidt-Matthiesen und Gunther Bastert*. 8 ed. Stuttgart: Schattauer; 2017: 439–446
- [21] Beckmann MW, Bader W, Bechtold I et al. Finanzierung und finanzielle Probleme von Leistungen und Strukturen im Fachgebiet Gynäkologie und Geburtshilfe im Jahr 2011 – DRG-System und stationäre Versorgung inklusive Urogynäkologie und benignen wie auch malignen gynäkologischer Operationen. *Geburtshilfe Frauenheilkd* 2011; 71: 497–510
- [22] Lux M, Hildebrandt T, Beyer-Finkler E et al. Relevance of Health Economics in Breast Cancer Treatment – the View of Certified Breast Centres and Their Patients. *Breast Care* 2013; 8: 15–21. doi:10.1159/000347098
- [23] Barbier L, Declerck P, Simoens S et al. The arrival of biosimilar monoclonal antibodies in oncology: clinical studies for trastuzumab biosimilars. *Br J Cancer* 2019; 121: 199–210. doi:10.1038/s41416-019-0480-z
- [24] Hübel K, Kron F, Lux MP. Biosimilars in oncology: Effects on economy and therapeutic innovations. *Eur J Cancer* 2020; 139: 10–19. doi:10.1016/j.ejca.2020.07.037
- [25] Cesarec A, Likić R. Budget Impact Analysis of Biosimilar Trastuzumab for the Treatment of Breast Cancer in Croatia. *Appl Health Econ Health Policy* 2017; 15: 277–286. doi:10.1007/s40258-016-0285-7
- [26] Cuellar S. Integrating trastuzumab biosimilars and HER2-directed therapies into HER2-positive breast cancer management. *Am J Manag Care* 2020; 26 (Suppl 2): S32–S40. doi:10.37765/ajmc.2020.42900